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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,896	RABINOVSKY ET AL.	
	Examiner	Art Unit	
	Paul Dowell	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-16,25,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-24, 26-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/27/04, 10/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-40 are pending.

Election/Restrictions

Applicant's election of claims 17-38 (group II), SEQ ID NO:1 and stimulating angiogenesis as the goal of the claimed treatment method in the response on 2/2/2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that Applicants were not entirely responsive to the restriction requirement of 11/30/2005. Specifically, on page 4 of the restriction requirement of 11/30/2005:

> Upon election of group II, Applicant's are further required to elect: one cell type from the group consisting of somatic cells, stem cells or germ cells as recited in claim 32. It is noted that this is a restriction requirement and not a species election since the different cell types recited in claim 32 are structurally and functionally distinct.

Applicants have not responded to this specific restriction requirement. However, it is noted that the restriction requirement of 11/30/2005 has been modified to rejoin all cell types with the invention of Group II. The restriction requirement of 11/30/2005 modified as such is still deemed proper and is therefore made FINAL.

Claims 1-16, 39 and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claim 25 has also been withdrawn as being drawn to a nonelected invention because Applicants have elected examination of

SEQ ID NO:1 and claim 25 recites SEQ ID NO:2. Further, for the purposes of examination, claim 26 is interpreted to read on SEQ ID NO:1 only and not on SEQ ID NO:1 or SEQ ID NO:2 since Applicants have elected examination of SEQ ID NO:1. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/2/2006.

Claims 17-24, 26-38 are under examination in the instant office action.

Claim Objections

Claims 17-24 and 26-38 are objected to for being drawn to a non-elected invention. Specifically, Applicants have elected "stimulating angiogenesis" as the goal of the claimed treatment method recited in claim 17 and as such claim 17 and dependent claims 18-24 and 26-38 are examined only to the extent that they read on a method for stimulating angiogenesis in a subject. Applicants are required to delete the non-elected subject matter from the instant claim.

Claim 26 is objected to for being drawn to a non-elected invention. Specifically, Applicants have elected SEQ ID NO:1 and as such claim 26 is examined only to the extent that it reads on SEQ ID NO:1. Applicants are required to delete the non-elected subject matter from the instant claim.

Specification

The specification is objected to for the following reasons:

The specification on page 48, paragr. 0162, lines 9-12 recites, "The results shown in Figure 6 indicate that IGF-I plasmid mediated supplementation using a

construct that stimulates the secretion of the transgene product into the general circulation does not affect ***MyoD*** expression in the treated muscle" (emphasis added). However, the title of Figure 6 recites, "Induction of myogenin" and the specification on page 14, paragr. 0036 recites, "Figure 6 shows expression of myogenin". MyoD and myogenin are distinct myogenic transcription factors with distinct structure and function (for example see page 49, paragr. 0165, last three lines of the specification) and the instant recitation of the specification is inconsistent with the data presented in Figure 6.

Claim Rejections - 35 USC § 112

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-24, 26-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for stimulating angiogenesis in a subject comprising:

directly injecting into a muscle tissue of the subject an isolated nucleic acid expression construct,

wherein the muscle tissue comprises cells,

wherein the isolated nucleic acid expression construct comprises: a myogenic promoter, a nucleic acid sequence encoding IGF-I and a 3' UTR,

wherein the isolated nucleic acid expression construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and the 3'UTR are operably linked,

thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct, thereby expressing said encoded IGF-I in said cells and thereby stimulating angiogenesis in the muscle of said subject.

does not reasonably provide enablement for:

A method for stimulating angiogenesis in a subject comprising:

delivering into any tissue of the subject an isolated nucleic acid expression construct by any route or mode of delivery,

wherein said any tissue comprises cells,

wherein the isolated nucleic acid expression construct comprises: any fragment of a myogenic promoter and any nucleic acid sequence encoding any fragments of IGF-I,

wherein the isolated nucleic acid expression construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and the 3'UTR are operably linked;

thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct, thereby expressing said encoded IGF-I in said cells and thereby stimulating angiogenesis in the muscle of said subject.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discloses construction of vectors for expressing human IGF-I in a muscle specific fashion by operably linking nucleic acid encoding said human IGF-I to myogenic promoters. The specification discloses that, depending upon which 3'UTR is included in said vectors, human IGF-I can be expressed at high levels in muscle wherein said human IGF-I is either secreted (when

operably linked to a growth hormone releasing hormone 3'UTR) or retained within the cells of the muscle (when operably linked to a skeletal alpha actin 3'UTR). The specification discloses that intramuscular injection of said vectors into mice induces expression of proteins (e.g. VEGF, FLT-1, myogenin, MyoD, FLK-1) that are typically associated with an angiogenic response.

The breadth of independent claim 17 is such that it reads on a method of stimulating angiogenesis in a subject comprising delivering into any tissue of the subject an isolated nucleic acid expression construct wherein said nucleic acid expression construct comprises a myogenic promoter operably linked to a nucleic acid encoding IGF-I. The art of record at the time of the invention is replete with teachings (for example see Coleman **(Journal of Biological Chemistry, 270:12109-12116, 1995, IDS)**, Draghia-Akli **(Nature Biotechnology, 17:11791183, 1999, IDS)**, Fewell et al **(Molecular Therapy, 3:574-583, 2001, IDS)** and Isner **(U.S. Patent 6,121,246)**) demonstrating that myogenic promoters drive expression of operably linked nucleic acids in muscle and not other tissues (e.g. spleen, skin, brain, etc.). Thus, it is questionable whether delivering said isolated nucleic acid expression construct to the spleen, for example, would result in expression of IGF-I thereby inducing angiogenesis. This is also true for any somatic cells, stem cells or germ cells and it is noted that claim 32 recites, "wherein the cells of the subject are somatic cells, stem cells, or germ cells". The specification and the art of record at the time of the invention are enabling only for directing muscle-specific expression of nucleic acids operably linked to myogenic promoters.

The specification describes working examples where human full-length wild-type IGF-I was delivered and expressed in muscle tissue. The specification provides no specific guidance or working examples as to how an artisan would practice the claimed invention with a nucleic acid encoding any IGF-I (e.g. any fragments or derivatives of IGF-I). Claim 17 recites, "a nucleic acid sequence encoding an IGF-I or functional biological equivalent thereof"; claim 19 recites, "wherein the encoded IGF-I or functional biological equivalent thereof has an amino acid sequence that is at least 85% identical to SEQ ID NO: 4"; claim 24 recites, "wherein a construct nucleic acid sequence is at least 90% identical to SEQ ID NO:1". The breadth of the instant claims is not enabled for the following reasons.

The art of record at the time of the invention is replete with teachings of IGF-I protein structure and function and the mechanisms of IGF-I signaling through both insulin and IGF-I receptors (for example see **Laron, Journal of Clinical Pathology: Molecular Pathology, 54:311-316, 2001** and **Van Obberghen et al, Eurpopean Journal of Clinical Investigation, 31:966-977, 2001**). It was well known at the time of the invention that IGF-I possesses cysteine residues that participate in disulfide bond formation and that said disulfide bond formation is important for proper protein folding and the resultant tertiary structure required for proper biological function, as taught by Milner et al **(Biochemistry Journal, 308:865-871, 1995)**, for example (see Abstract; page 865, col. 1, paragr. 1). The instant claims read, for example, on IGF-I derivatives lacking one or more of the cysteine residues that are important for proper folding

and the resultant biological function of IGF-I. The specification provides no guidance as to how an artisan would know which of said IGF-I derivatives would be operant in the instantly claimed invention.

Further, claim 24 recites, "wherein a construct nucleic acid sequence is at least 90% identical to SEQ ID NO:1". Claim 24 reads on a nucleic acid construct wherein the entire IGF-I encoding nucleic acid fragment is replaced with a nucleic acid of any nucleotide composition. In other words, the nucleic acid sequence of SEQ ID NO:1 contains 5423 nucleotides and a nucleic acid sequence that is 90% identical to SEQ ID NO:1 would tolerate replacement of up to approximately 542 nucleotides. The nucleotide sequence encoding IGF-I being approximately 461 nucleotides, claim 24 reads on a nucleic acid construct that doesn't even encode IGF-I. The specification provides no guidance as to how an artisan would make or use the claimed invention as such.

In summary, an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate in scope with the instant claims. Such experimentation will be undue because of the unpredictability of expressing a nucleic acid in any tissue when said nucleic acid is operably linked to a myogenic promoter and the unpredictability of practicing the claimed invention with any IGF-I derivative. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to practice the claimed invention.

Thus, limiting the scope of the claims to:

A method for stimulating angiogenesis in a subject comprising:

directly injecting into a muscle tissue of the subject an isolated nucleic acid expression construct,

wherein the muscle tissue comprises cells,

wherein the isolated nucleic acid expression construct comprises: a myogenic promoter, a nucleic acid sequence encoding IGF-I and a 3' UTR,

wherein the isolated nucleic acid expression construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and the 3'UTR are operably linked,

thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct, thereby expressing said encoded IGF-I in said cells and thereby stimulating angiogenesis in the muscle of said subject, is proper.

Written description

Claims 17-24 and 27-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses: a method for stimulating angiogenesis in a subject comprising delivering into a tissue of the subject an isolated nucleic acid expression construct, wherein said nucleic acid expression

construct comprises a nucleic acid sequence encoding an insulin-like growth factor I (IGF-I) or functional biological equivalent thereof.

The specification defines "IGF-I or functional biological equivalent thereof" as follows:

> In terms of "functional biological equivalents", it is well understood by the skilled artisan that, inherent in the definition of a "biologically functional equivalent" protein and/or polynucleotide, is the concept that there is a limit to the number of changes that maybe made within a defined portion of the molecule while retaining a molecule with an acceptable level of equivalent biological activity. Functional biological equivalents are thus defined herein as those proteins (and polynucleotides) in which selected amino acids (or codons) may be substituted. ***A peptide comprising a functional biological equivalent of IGF-I (SEQID NO.: 4) is a polypeptide that is engineered to contain distinct amino acid sequences while simultaneously having similar or improved biological activity when compared to IGF-I (SEQID NO.: 4)***. Thus, in one embodiment of the encoded IGF-I or functional biological equivalent thereof has an amino acid sequence of SEQID No: 4, or SEQD No.: 4 with conservative amino acid substitutions. In another embodiment, a preferred IGF-I peptide comprises an amino acid sequence that is at least 85% identical to SEQD No.: 4, wherein the biological activity is preserved or enhance. For example, one biological activity of IGF-I is to stimulate angiogenesis in a subject. (page 43, paragr. 0147; emphasis added)

Such would encompass a large number of variants and molecules that are functional biological equivalents of IGF-I. However, the specification only discloses full-length human IGF-I.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, full-length human IGF-I is the only species whose complete structure is disclosed. While the genus encompasses a large number of variants and molecules that are functional biological equivalents of IGF-I the specification does not describe the complete structure of a representative number of species of the large genus.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that a functional biological equivalent of IGF-I have "similar or improved biological activity when compared to IGF-I (SEQID NO.: 4)". Such a functional limitation cannot be an identifying characteristic for the claimed diverse genus of molecules since, by Applicant's definition of a functional biological equivalent of IGF-I, all members of the claimed genus will have that characteristic.

Claims 18-24 and 27-38 depend directly or indirectly from claim 17 but do not remedy the reasons for the instant rejection. Therefore, claims 18-24 and 27-38 are likewise rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Further, Applicant's attention is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In conclusion, Applicant's disclosure of one species (i.e. full-length human IGF-I) of the claimed broad genus of functional biological equivalents of IGF-I is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-24, 26-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is incomplete. Claim 17 is drawn to:

A method for stimulating angiogenesis in a subject comprising:

Delivering into a tissue of the subject an isolated nucleic acid expression construct,

wherein the tissue comprises cells,

wherein the isolated nucleic acid expression construct comprises: a myogenic promoter, a nucleic acid sequence encoding an IGF-I or functional biological equivalent therof and a 3' untranslated region,

wherein the isolated nucleic acid expression construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and the 3'UTR are operably linked; and the isolated nucleic acid expression construct has an

in vivo expression activity for the encoded IGF-I or functional equivalent thereof in the tissue of the subject.

However, the instant claim does not recite any positive steps which clearly relate back to the preamble. Therefore, it is unclear how the recited step relates to the method for stimulating angiogenesis in a subject and whether the goal of said method has been resolved. Further, claims 18-24, 26-38 depend either directly or indirectly from claim 17 and are likewise rejected.

Claim 23 contains a contradictory recitation. To clarify, claim 17 recites, "wherein the isolated nucleic acid expression construct ***is substantially free from a viral backbone***" (emphasis added). Claim 23 depends indirectly from claim 17 and recites, "wherein the transfection-facilitating vector system is a plasmid, ***a viral vector***, a liposome, or a cationic lipid" (emphasis added). As such, claim 23 appears to further limit an expression construct that is substantially free from a viral backbone to an expression construct that is a viral vector.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 19-23, 31-38 rejected under 35 U.S.C. 102(b) as being anticipated by Coleman et al **(Journal of Biological Chemistry, 270:12109-12116, 1995, IDS)**.

Coleman teaches a method of delivering a plasmid construct comprising a nucleic acid encoding IGF-I into the muscle tissue of mice. Specifically, Coleman

teaches a method of generating transgenic mice that exhibit muscle cell specific expression of IGF-I (page 12110: col. 1, paragr. 4 to col. 2, line 7). The plasmid construct taught by Coleman used to generate the transgenic mice comprises the avian skeletal α-actin myogenic promoter region and the avian skeletal α-actin myogenic 3'UTR operably linked to the nucleic acid coding region of human IGF-I (page 12110, col. 1, paragr. 2). Coleman teaches that said transgenic mice exhibit muscle specific expression of human IGF-I (page 12112: col. 1, paragr. 3; Fig. 4) and as such the plasmid DNA construct taught by Coleman was delivered into the muscle tissue of said transgenic mice.

Please note that intended use limitations bear little weight on the determination of patentability. In the instant case, for claim 17, the limitation "a method for stimulating angiogenesis" does not carry patentable weight in the determination of anticipation for the claimed products. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art. In a claim drawn to a process, the intended use must result in a manipulative difference as compared to the prior art. See MPEP § 2111.02, *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, since the method steps recited in the instant claim(s) and the method steps taught by Coleman are the same, practice of the process would inherently result in the same outcome.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-24, 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman **(Journal of Biological Chemistry, 270:12109-12116, 1995, IDS)** in view of Draghia-Akli **(Nature Biotechnology, 17:11791183, 1999, IDS)**, Fewell et al **(Molecular Therapy, 3:574-583, 2001, IDS)** and Isner **(U.S. Patent 6,121,246)**.

The teachings of Coleman are put forth herein above under the 35 U.S.C. 102(b) rejection.

Coleman does not teach a myogenic promoter comprising a nucleic acid sequence that is at least 85% identical to SEQ ID NO:3 (i.e. the synthetic

myogenic promoter termed SPc5-12), does not teach a nucleic acid construct comprising the nucleotide sequence of SEQ ID NO:1 and does not teach transfection enhancing techniques/compounds such as electroporation or transfection facilitating polypeptides as a means to deliver nucleic acids to cells.

Draghia-Akli teaches a myogenic promoter consisting of the nucleic acid of SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12). Draghia-Akli teaches a plasmid construct comprising the SPc5-12 promoter operably linked to a nucleic acid encoding human growth hormone releasing hormone (GHRH; page 1182, col. 2, paragr. 3). Draghia-Akli teaches intramuscular injection of said plasmid construct into pigs and then electroporating the injected muscle of said pig to more efficiently deliver said plasmid to the muscle cells (page 1180: col. 1, paragr. 4, line 1 to col. 2, line 10). Draghia-Akli teaches that said SPc5-12 promoter is a powerful synthetic muscle promoter that drives high level expression of operably linked heterologous nucleic acids in a muscle-specific manner (page 1180, col. 1, lines 1-2).

Fewell teaches instramuscular injection of plasmid DNA complexed with the charge polypeptide poly-L-glutamate into mice followed by electroporation. Fewell teaches that injection of a plasmid comprising a nucleic acid encoding factor IX and that injection of a plasmid comprising a nucleic acid encoding erythropoietin as such (i.e. forming a complex comprising said plasmids and poly-L-glutamate prior to injection) resulted in enhanced expression of said plasmids compared to when said plasmids were injected as saline solution (i.e. when said plasmids were not complexed with poly-L-glutamate). Thus, Fewell

teaches that intramuscular injection of plasmid DNA complexed with poly-L-glutamate followed by electroporation results in more efficient transfection of the cells within the injected muscle.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the method of Coleman with a reasonable expectation of success by: 1) interchanging the avian skeletal α-actin myogenic promoter with the strong muscle-specific synthetic SPc5-12 promoter taught by Draghia-Akli, 2) complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection of said plasmid DNA as taught by Fewell and 3) subjecting muscle tissue injected with said plasmid DNA to electroporation as taught by both Draghia-Akli and Fewell with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to modify the method of Coleman as such because: 1) Draghia-Akli teaches that the synthetic SPc5-12 promoter drives high level, muscle-specific expression of operably linked nucleic acids, 2) Fewell teaches that complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection and prior to electroporation results in enhanced uptake of said plasmid DNA and 3) both Draghia-Akli and Fewell teach that electroporating muscle after intramuscular injection of plasmid DNA results in enhanced uptake of said plasmid DNA. Increased cellular uptake of plasmid DNA and increased expression of operably linked nucleic acids contained within said plasmid would be advantageous when practicing methods of gene therapy. Thus, the claimed invention as a whole was *prima facie* obvious.

Further, it is noted that pAV2001 (i.e. SEQ ID NO:1 of the instant application) is a hybrid plasmid consisting of fragments of the plasmids taught by Coleman and Draghia-Akli. The specification on page 42, lines 16-19 recites, "An Nco/HindIII fragment of a SIS II plasmid (Coleman et al., 1995), containing the IGF-I cDNA and the skeletal alpha actin 3'UTR, was cloned into the NcoI/KpnI sites of pSP-HV-GHRH (Draghia-Akli et al., 1999) to generate pSP-IGF-I-SK3'UTR (pAV2001 – SEQID No.: 1)." Thus, an artisan of ordinary skill at the time of the invention would have realized with a reasonable expectation of success that the teachings of Coleman and Draghia-Akli could be combined to generate the plasmid DNA consisting of the nucleic acid sequence of SEQ ID NO:1.

Please note that intended use limitations bear little weight on the determination of patentability. In the instant case, for claim 17, the limitation "a method for stimulating angiogenesis" does not carry patentable weight in the determination of anticipation for the claimed products. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art. In a claim drawn to a process, the intended use must result in a manipulative difference as compared to the prior art. See MPEP § 2111.02, *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, since the method steps recited in the instant claim(s) and the method steps taught by Coleman, Draghia-Akli and Fewell are the same, practice of the process would inherently result in the same outcome.

However, it is further noted that Isner teaches a method for stimulating angiogenesis in an ischemic muscle tissue in a human host comprising injecting into said tissue a DNA sequence encoding an angiogenic protein, wherein said DNA sequence comprises a promoter sequence, wherein the angiogenic protein is selected from a group of angiogenic proteins including insulin-like growth factor (IGF-I; claims 1 and 16; col. 4, lines 8-10, 23). The teachings of Isner provide additional motivation for an artisan of ordinary skill to use a nucleic acid encoding IGF-I to stimulate angiogenesis in muscle and further support that the claimed invention as a whole was *prima facie* obvious.

Conclusions

No claims are allowed.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment and provide any statements that might help to identify support for the claimed invention (e.g. if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Dowell whose telephone number is 571-272-5540. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on 571-272-0735. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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